IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Anderson
Serial No. 09/994,937
Filed November 28, 2001

Confirmation No. 7327
Group Art Unit 1616
Examiner Abigail Fisher

For SOLVENT SYSTEMS FOR PHARMACEUTICAL AGENTS

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF DAVID M. ANDERSON UNDER 37 C.F.R. 1.132

David M. Anderson declares as follows:

1. I am the inventor of the above-identified application. I hold a position in Lyotropic Therapeutics, Inc., the assignee of record of the above-identified application, as Vice President Scientific Affairs. I have read and understand the application, and I have read and understand the various office actions to date, the responses of the Applicant, and the references of record. I have previously submitted Declarations in this case, including one dated October 14, 2008, and the declarations I made therein about my experience, education, qualifications and expertise remain accurate and true.

2. In preparation for an interview with the Examiner on this case conducted on February 24, 2009, I prepared or had Lyotropic Therapeutics laboratory personnel under my direction and control prepare the following materials, take the following actions and made the following observations.

3. For the examples discussed, the cubic or hexagonal phase nature of the material can be reliably distinguished from liquid phases, such as in particular an L1 or L2 phase,

microemulsion, or L3 phase (sometimes called the "sponge phase"), by a number of methods. Macroscopically the reversed cubic liquid crystalline (as compared to liquid) phase nature of material can be determined by the clarity and high viscosity of the material. Microscopically, the reversed cubic (as opposed to liquid) phase nature of material in dispersion can be determined by the shape of the dispersed material, provided some particles are at least about 2 microns in size. As explained in the Specification and other Declarations on file in the case, additional means of determining the phase of the material are available, including optical textures in a polarizing microscope, and small angle X-ray scattering (SAXS). As for the lamellar phase, the reversed cubic or hexagonal phase can be reliably distinguished from the lamellar phase on the basis of the much lower, more liquid-like, viscosity of the latter, and by observation under the polarizing optical microscope (available in my lab), where the optical textures observed for lamellar phase is distinctly different from those of the reversed hexagonal phase, and in sharp contrast, none are present for the reversed cubic phase, since it is optically isotropic.

4. The following work is evidenced in a series of photographs I took, labeled as **Exhibit 1.** This work observes the impact of the addition of two selected essential oils on the reversed cubic phase material of Landh (US Patent No. 5,531,925), and by contrast on the reversed cubic phase material of the Invention.

(a) I prepared a reversed cubic phase of 60:40 GMO:water, as per the Landh specification. I then added 15% spearmint oil. The addition of spearmint oil caused the material to lose viscosity and clarity, that is, to flow much more freely and to become milky and strongly inhomogeneous, both indications of the transformation away from reversed cubic phase toward liquid (i.e., L1, L2, microemulsion, or L3) phase. The addition of the spearmint oil destroyed the reversed cubic phase nature of the material, in favor of liquid phase.

(b) I prepared a reversed cubic phase of 60:40 GMO:water as per the Landh specification. I then added clove oil to a level of 15%. Again, the addition of spearmint oil caused the material to lose viscosity and to become inhomogeneous and milky, both

indications of the transformation away from reversed cubic phase toward a liquid phase. The addition of the oil destroyed the reversed cubic phase in favor of the liquid phase.

(c) I prepared a mixture of 70:30 Pluronic L122:water, which formed reversed cubic phase material. I then added spearmint oil to a level of 20%. The material remained clear and highly viscous, as well as optically isotropic, indicating it remained cubic.

(d) I prepared a reversed cubic phase of 70:30 Pluronic L122:water. I then added clove oil to a level of 20%. The material remained clear and highly viscous, as well as optically isotropic, indicating it remained cubic.

5. I recorded a short video of one of my lab assistants stirring the ultimate material prepared in Paragraph 4(a) and 4(c) above. The clip was provided to Examiner Fisher in advance of the interview. The video shows in real time: (i) the notably fluid and milky nature of the material produced by a combination of the Landh reversed cubic phase material and the selected essential oil, indicating the shift away from reversed cubic liquid crystalline phase to liquid; and (ii) by contrast, the continued high viscosity and clarity of the material produced by combination of a reversed cubic phase of the invention with the selected oil, indicating it remains reversed cubic phase.

6. The following work is recorded in photographs I took labeled as **Exhibit 2**. I placed material resulting from the work described in Paragraph 4(a) in a test tube (marked "Landh"), and in a separate test tube place material from the work described in Paragraph 4(c) (marked "Anderson"). I centrifuged both test tubes for approx. 10 minutes at 3,000 RPM. The two phase nature of the material from Paragraph 4(a) was evident, with mostly liquid phase present, due to the liquefaction of the reversed cubic phase by addition of the essential oil. The material from Paragraph 4(c) was reversed cubic phase.

7. The following work is recorded in photographs I took labeled as **Exhibit 3**.

(a) I dispersed 3gm of 60:40 GMO:water reversed cubic phase in 30mL of 0.6% Pluronic F-68 solution using a Brinkman Polytron homogenizer, in the manner of the Landh specification. I observed this with Differential Interference Contrast microscopy.

I selected for photomicrography larger particles which exhibited rectangular angular shape indicative of reversed cubic phase material and representative of the particulate material.

(b) To 4.5mL of the above dispersion I added 0.050g of spearmint oil and continued homogenizing. The spearmint added equaled approximately 1% w/w of the formulation, that is, the aqueous dispersion. I observed microscopically and selected for photomicrography clumpy and rounded particles which were representative of the particulate material after the addition of the essential oil. The size and shape is indicative of liquid material, not reversed cubic liquid crystalline material, and indicative of fusing and clumping of the particles. The dispersion of fine particles was ruined by the addition of essential oil.

8. The following work is recorded in photographs I took labeled as **Exhibits 4a and 4b**.

(a) I prepared a phosphatidylcholine ("PC"):water:spearmint oil reversed cubic phase, by combining 57:43 PC 90G:water, and then adding in 20% spearmint oil. The material formed was reversed cubic phase. Then, I increased the amount of oil added until the spearmint oil totaled 37% by weight. The material remained cubic, as indicated by the high degree of clarity, as well as optical isotropy and high viscosity.

(b) I prepared a PC:[water + glycerol]:vitamin E reversed cubic phase. I started by combining PC ("Phospholipon 90G" from Lipoid), water and alpha-tocopherol in the ratio of 30:45:25. While this material was mostly reversed cubic, some excess water was present making the clarity poor, in comparison with a typical cubic phase. Therefore approximately 15% of the polar, water-miscible solvent glycerol was added, which very quickly established a high degree of clarity in the material. The material was a reversed cubic phase, as indicated by the high degree of clarity as well as optical isotropy and high viscosity, and 10% more tocopherol was easily added to the material while retaining the cubic phase structure.

9. **Exhibit 5** is a table and graph I prepared collecting data I prepared over the years on the amount of paclitaxel solubilized by various reversed cubic phase formulations, made with varying amounts of essential oils as a component of the reversed cubic phase. The

graph shows that, near the Y-axis with little if any essential oils incorporated, there is little if any paclitaxel solubilized in a reversed cubic phase. However, moving to the right along the X axis, across increasing amounts of the essential oil in the reversed cubic phase, the data shows increasing amounts of paclitaxel can be incorporated in the reversed cubic phase with the addition of more essential oils.

10. **Exhibit 6** is a generic phase diagram showing the range of different and distinct lyotropic liquid and liquid crystalline phase materials and their very different morphologies, and illustrating that many different phases of thermodynamically stable nanostructured material may form from the combination of the same ingredients in different ratios. The different morphologies of the different phases give rise to very different characteristics and properties, and greatly impact use in drug delivery.

11. **Exhibit 7** is a phase diagram of a system comprised of water, tocopherol (fat vitamin) and phosphatidylcholine. This system does not form reversed cubic phase in the absence of tocopherol. The phase diagram shows that with the addition of tocopherol a reversed cubic phase region is possible. However, the reversed cubic phase will not form with under 25% w/w of tocopherol in this system, and although a reversed hexagonal phase forms at lower levels of tocopherol, this phase cannot exist in equilibrium with excess water and is thus of very limited utility in the pharmaceutical approaches under focus in my work.

12. **Exhibit 8** is a phase diagram of a system comprised of water, essential oil of spearmint and phosphatidylcholine. This system does not form reversed cubic phase in the absence of spearmint oil. The phase diagram shows that with the addition of spearmint oil a reversed cubic phase region is possible. However, the reversed cubic phase will not form with under 18% w/w of spearmint oil, and although a reversed hexagonal phase forms at lower levels of spearmint oil, this phase cannot exist in equilibrium with excess water and is thus of very limited utility in the pharmaceutical approaches under focus in my work..

13. The mere combination of one or more of the hundreds of essential oils identified in Benet with the Landh dispersion of particles would not yield the material of the invention. In arriving at the invention, I sampled hundreds of different excipient compounds in hundreds of combinations and ratios to determine whether any would improve solubilization of the pharmaceutical compound, and at the same time enable the establishment or maintenance of the sought-after reversed cubic or hexagonal phase nature of the material, rather than destroying it. Those few which I discovered I have identified in the current specification. As I described in detail in my Declaration of October 14, 2008 it is because of their unusual chemical structure that the have a surprising two-fold effect that combine to enable the practice of the invention: "first to create a more favorable local milieu for the drug molecules and thus enable incorporation of hard-to-solubilize drugs; and, second, to increase the radius of curvature of the lipid layer, thus promoting the formation or maintenance of reversed cubic or reversed hexagonal phase material".

14. Armed with the specification, creating the materials of the invention is well within the competency of one of ordinary skill in the applicable art, using the systematic techniques identified in the specification and well known in the art. This was confirmed by Dr. Richard Templer in his Declaration filed in this case June 7, 2007.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

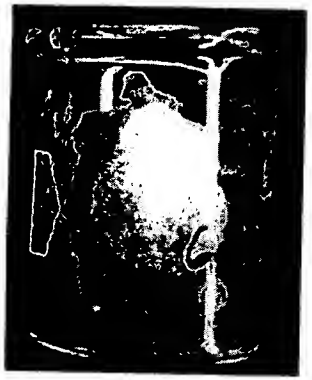
David M. Anderson, Ph.D.

March 26, 2009

Date

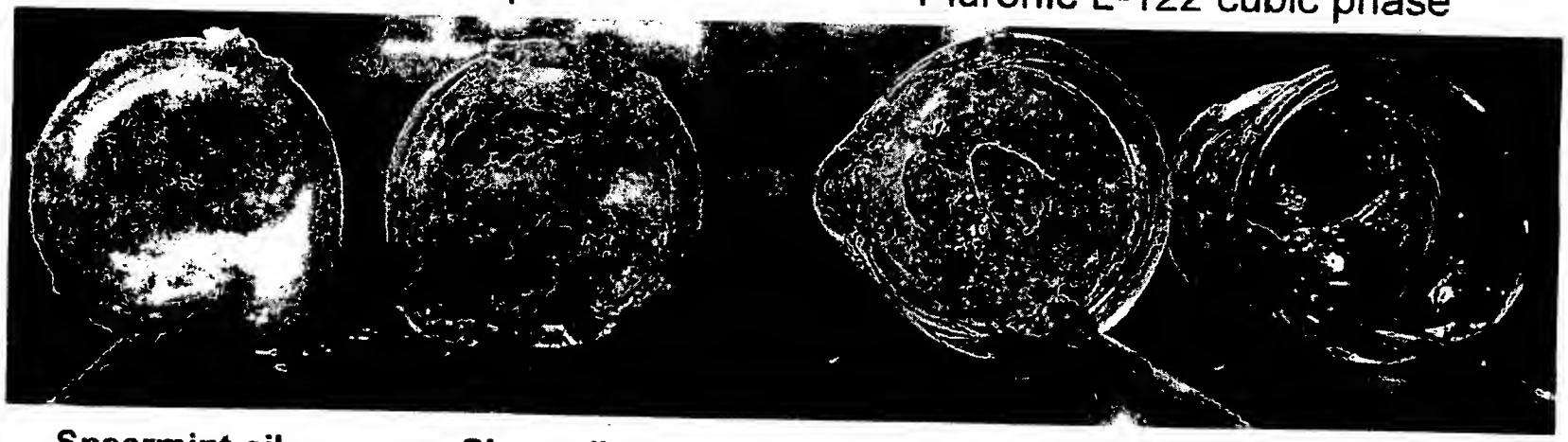
EXHIBIT 1

ADDITION OF TWO ESSENTIAL OILS TO THE REVERSED CUBIC PHASE MATERIAL OF U.S. PATENT 5,531,925 AND TO LANDH REFERENCED IN ITEM 4.



Landh-Larsson cubic phase

Pluronic L-122 cubic phase



Spearmint oil **Clove oil** **Spearmint oil** **Clove oil**

EXHIBIT 2

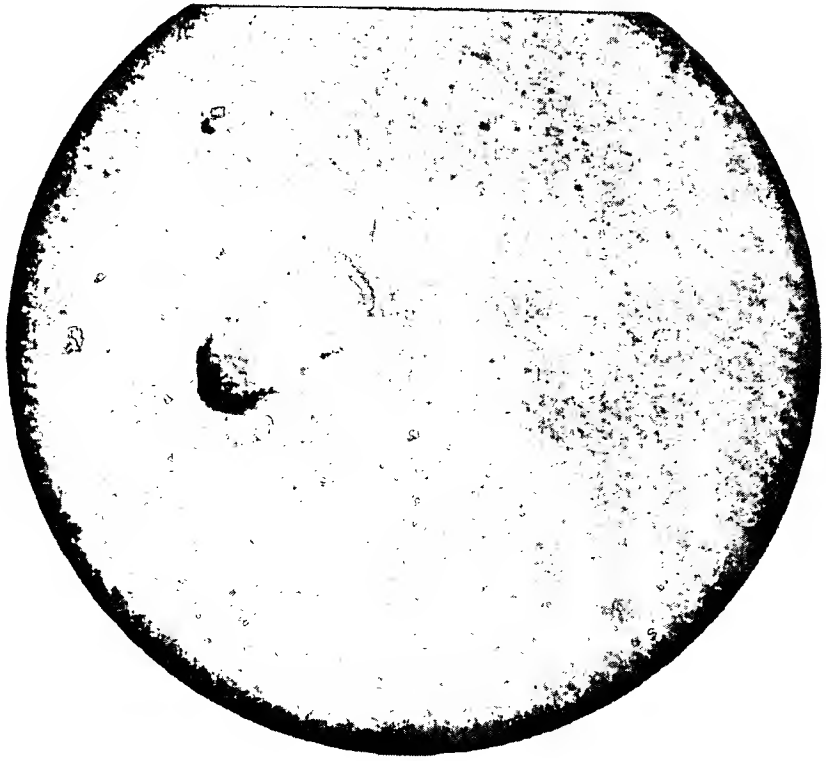
TEST TUBES MARKED AS "ANDERSON" AND "LANDH" REFERENCED IN ITEM 6

EXHIBIT 3

DIFFERENTIAL INTERFERENCE CONTRAST MICOGRAPHY IMAGES REFERRED TO IN ITEM 7

GMO / Water / F-68 Landh-Larsson Dispersion

Before essential oil



After spearmint oil

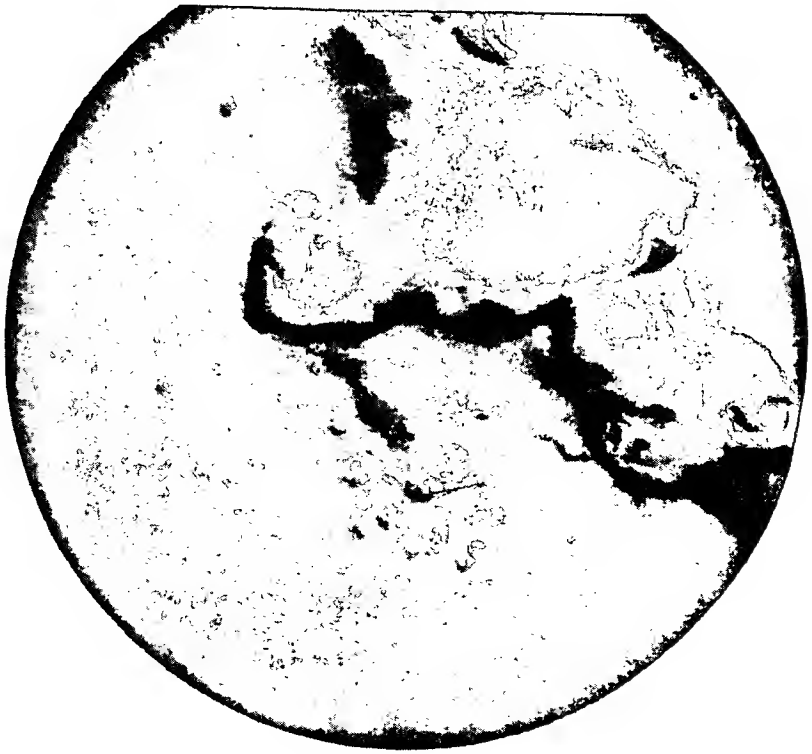


EXHIBIT 4A

PC:WATER:SPEARMINT OIL REVERSED CUBIC PHASE WITH THE ADDITION OF 20% SPEARMINT OIL; REFERENCED IN ITEM 8A

EXHIBIT 4B

PC:WATER+GLYCEROL:VITAMIN E REVERSED CUBIC PHASE WITH THE ADDITION OF 10% MORE TOCOPHEROL; REFERENCED IN ITEM 8B

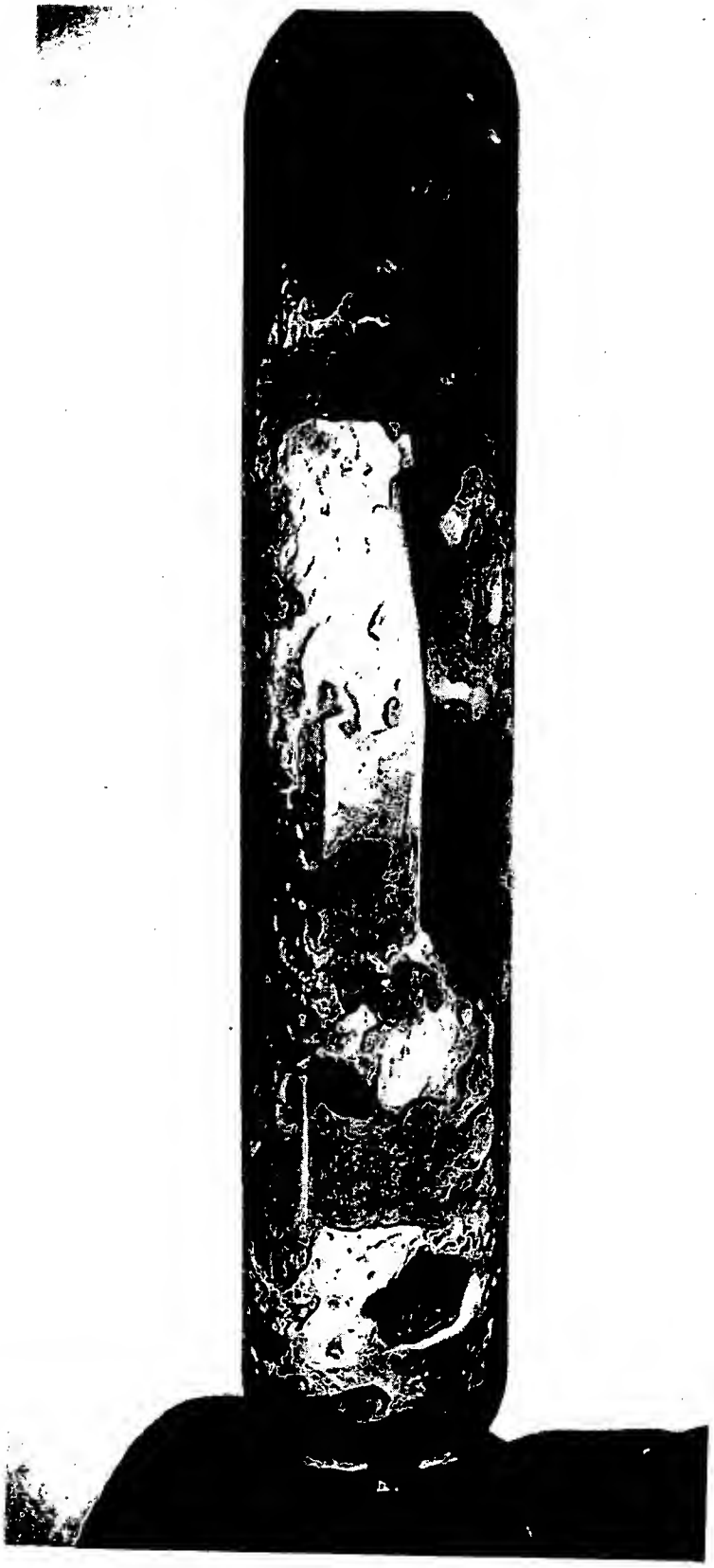


EXHIBIT 5

GRAPH DESCRIBED IN ITEM 9

%oil in Q	%pac in G	Date race
23.7	2.00	3/16/2006
46.2	3.00	11/16/2004
41.3	3.10	3/24/2004
42.3	2.75	3/21/2004
44.0	4.40	3/15/2004
44.0	3.96	9/7/2004
42.0	4.20	9/2/2004
44.0	3.00	3/13/2004

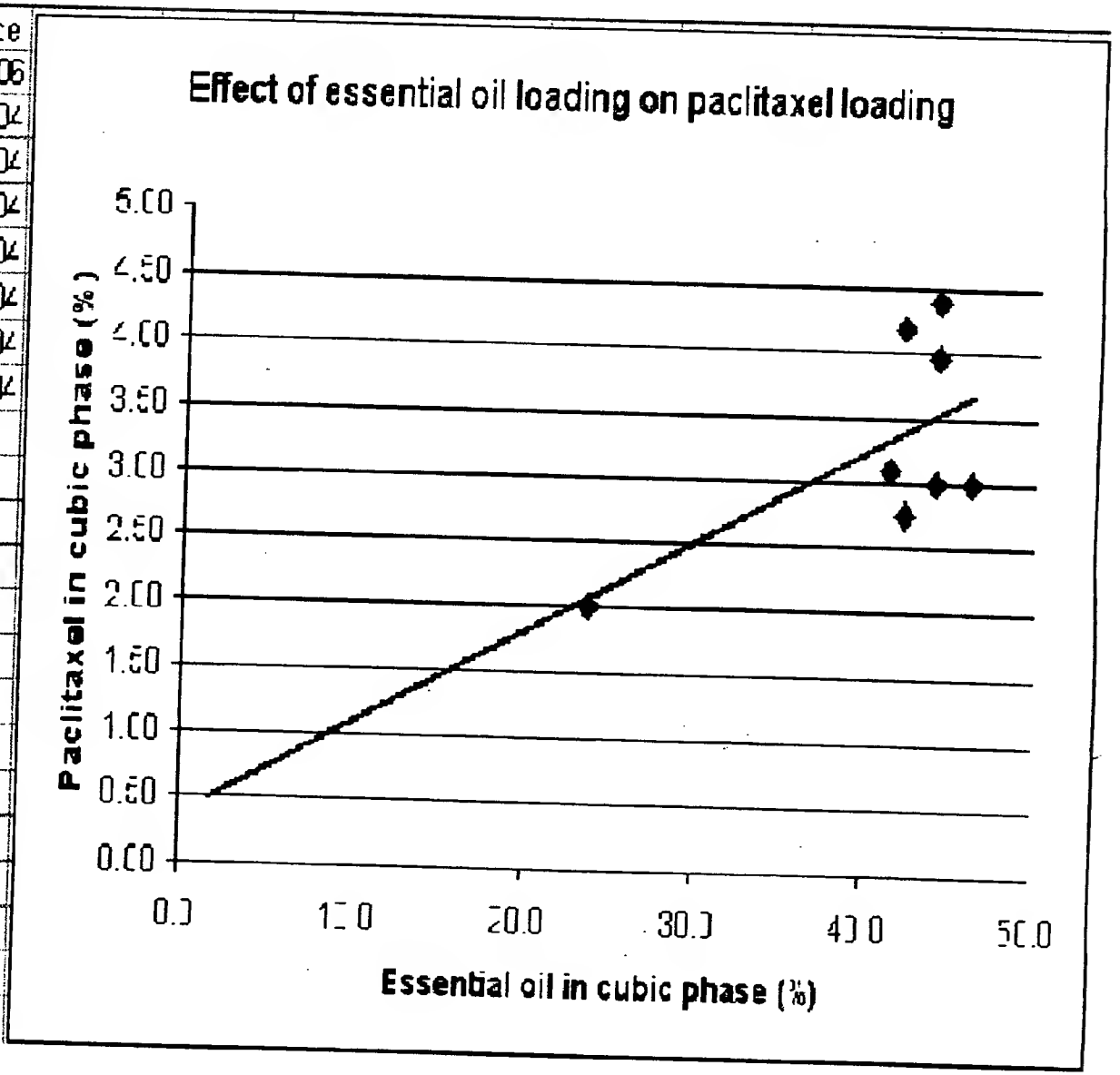


EXHIBIT 6

PHASE DIAGRAM OF DIFFERENT AND DISTINCT LYOTROPIC LIQUID AND LIQUID CRYSTALLINE PHASE MATERIALS; REFERENCED IN ITEM 10

Lyotropic Liquid and Liquid Crystalline Phases

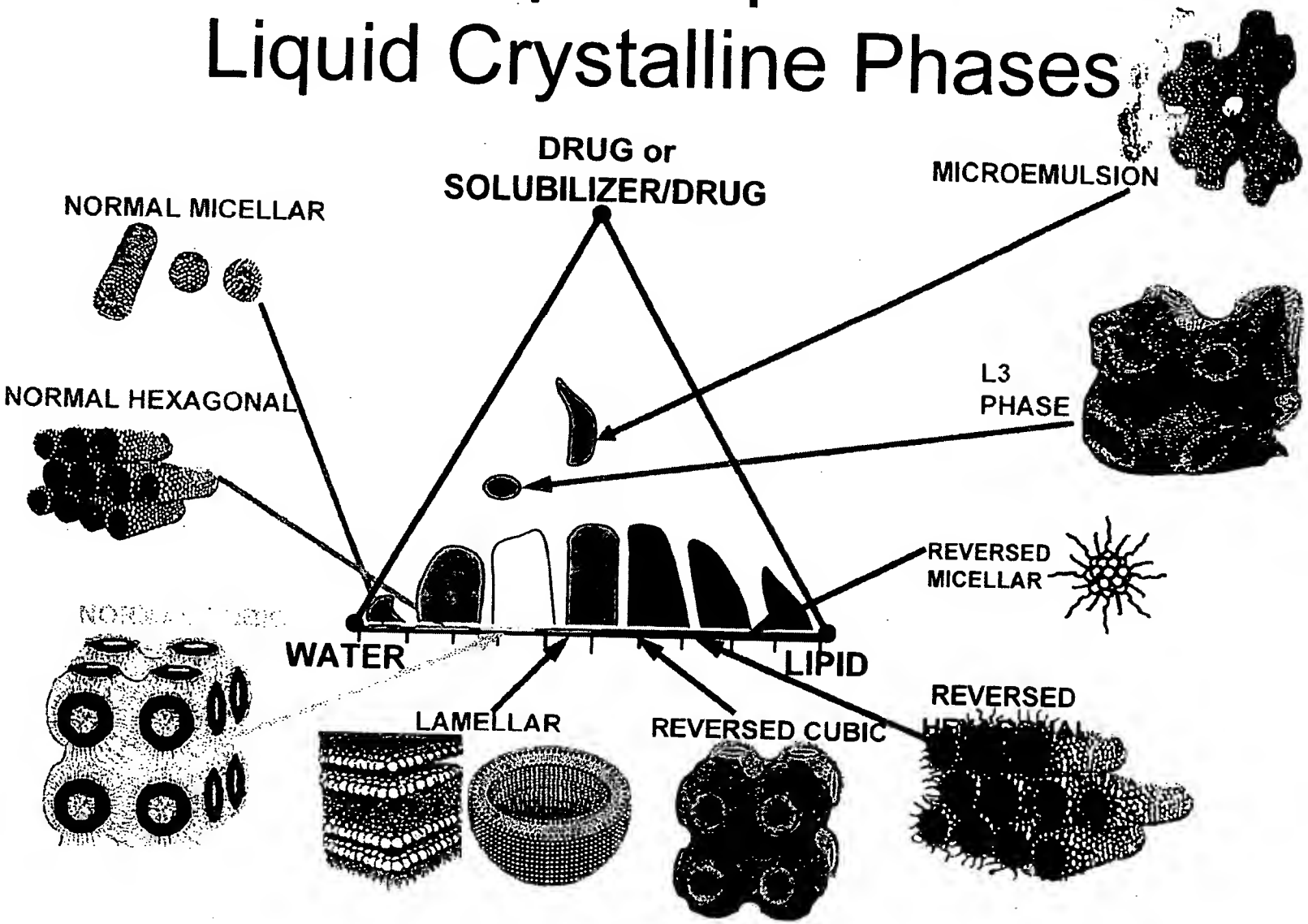


EXHIBIT 7

PHASE DIAGRAM OF WATER, TOCOPHEROL AND PC; REFERENCED IN ITEM OF 11

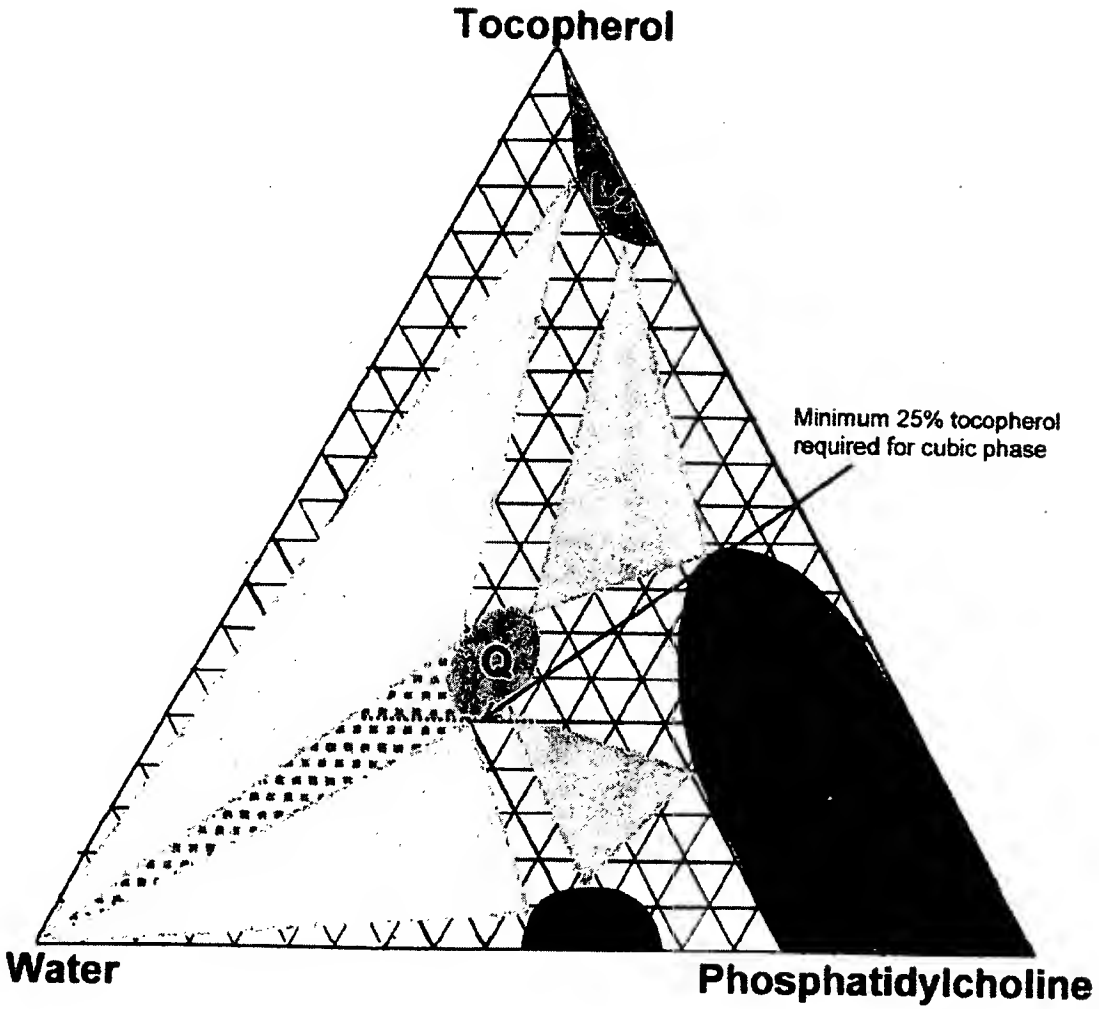
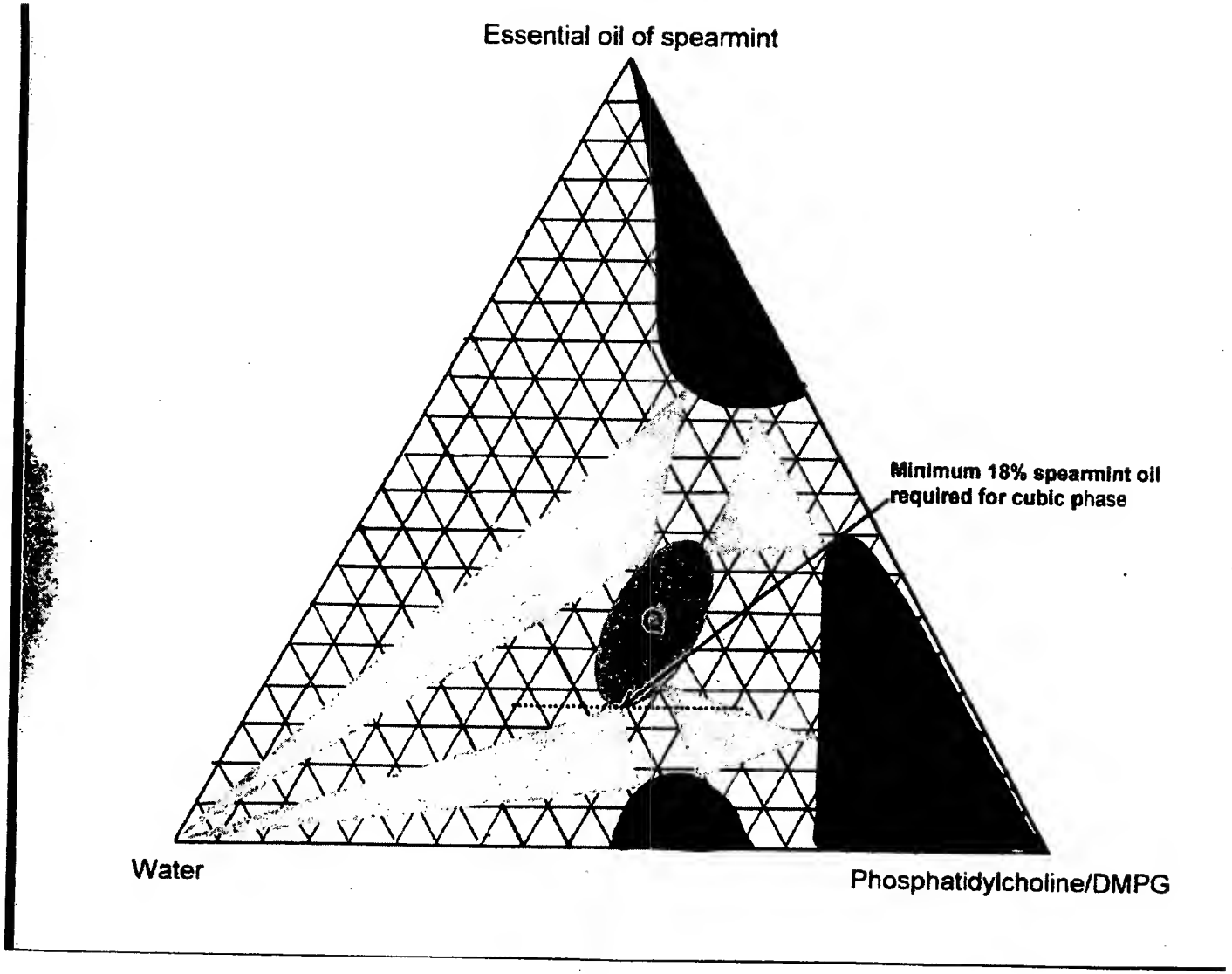

Tocopherol
Minimum 25% tocopherol
required for cubic phase
Q
Water
Phosphatidylcholine

EXHIBIT 8

PHASE DIAGRAM OF WATER, SPEARMINT OIL AND PC; REFERENCED IN ITEM OF 12


Essential oil of spearmint
Minimum 18% spearmint oil required for cubic phase
Water
Phosphatidylcholine/DMPG